REMARKS

Applicant respectfully requests reconsideration of this application in view of the amendments and remarks made herein.

Claims 34-70 are pending. Claims 34-70 have been canceled and replaced with new claims 71-98. The claims have been added to more particularly point out and distinctly claim the subject matter of the invention. Applicant respectfully submits that the added claims are supported by the original disclosure of this application. For examples, descriptive support can be found in the specification at page 3, lines 2-3; page 5, lines 6-10 and 22-24; page 6, lines 19-20; page 7, lines 2-8 and 13-15; page 8, lines 4, 7, 8 and 17-27; page 9, lines 1-3; page 11, lines 4-14; page 16, lines 13-18 and 22-26; page 17, lines 10-17; and the original claims 6, 9 and 20 as filed. In particular, the recitation of "without concomitant chemotherapy or radiation therapy" in claim 71 is supported by the specification at page 5, lines 6-10, disclosing tumor therapy with an anti-EGFR antagonist, in contrast with page 5, lines 11-13 and page 17, lines 18-21, specifically disclosing combination therapy. As such, no new matter has been added by these amendments.

Applicant thanks the Examiner, Anne L. Holleran, for the courtesies extended to Applicant's representatives during the interview of April 12, 2006.

APPLICANT'S STATEMENT ON SUBSTANCE OF EXAMINER'S INTERVIEW

Applicant's representatives gave an overview of the invention, and then identified various features of the pending claims which Applicant believes are not contained in, or rendered obvious by, the references cited by the Examiner. Applicant's positions are summarized below. Although no agreement was reached, the Examiner indicated she would further consider the Applicant's arguments upon receipt of this paper.

SUMMARY OF THE CLAIMED INVENTION

The presently claimed invention is directed to methods for inhibiting the growth of refractory tumors in patients that have previously been treated with a chemotherapeutic agent or radiation and which ***that have failed or have been resistant to such previous treatments***, comprising the administration of an anti-EGFR antibody or fragment thereof. Such refractory tumors are associated with a rapid disease progression and a poor prognosis. Prior to the present invention, once a patient's cancer became refractory, there were essentially no established treatment options with demonstrated efficacy. See, Saltz, et al., p.1201(2004,

Journal of Clinical Oncology 22:1201-1208: "Exhibit A") and Cunningham et al., p.344 (2004, N. Engl J Med 351:337-45: "Exhibit B"). The present invention represents a major medical advance in providing physicians with means for successful therapy of refractory tumors.

The present invention is supported by clinical data demonstrating the successful treatment of refractory colorectal cancer, in the absence of concomittant chemotherapy or radiation treatment, through the use of an anti-EGFR. See, Exhibit A and Exhibit B.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 40 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicant has canceled claim 40, without prejudice to the prosecution of the subject matter in a separate continuing application. Accordingly, Applicant respectfully requests withdrawal of this ground of rejection.

THE REJECTION UNDER 35 U.S.C. § 102(a) FOR ANTICIPATION

Claims 34-39, 41-44, 49-52 and 70 are rejected under 35 U.S.C. § 102(a) as being anticipated by Perez-Soler et al. (34th Annual Meeting of the American Society of Clinical Oncology 17:393 (May 16, 1998); "Perez-Soler") taken with the evidence of Herbst et al. (Expert Opin. Biol. Ther., 1:719-732 (2001): "Herbst"). The Examiner contends that Perez-Soler teaches the administration of an anti-EGFR antibody (C225) to patients having recurrent head and neck cancer resulting in two transient minor responses. Thus, according to the Examiner, Perez-Soler teaches the claimed methods.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984).

Applicant has amended the claims to specify that the anti-EGFR receptor antagonist is administered **without concomittant chemotherapy or radiation therapy**. In contrast, Perez-Soler teaches the administration of the C225 anti-EGFR antibody **in combination** with

administration of cisplatin. Given the difference between the teachings of Perez-Soler and the presently claimed invention, Perez-Soler cannot anticipate the presently claimed invention. Thus, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 102(a) be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) FOR OBVIOUSNESS

Claims 34-36, 39, 41-44, 48-51, 54 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yang et al. (Cancer Res. 59:1236-1243 (1999),"Yang") in view of Prewett et al., (Journal of Immunotherapy 19:419-427 (1997); "Prewett"). In particular, the Examiner contends that Yang demonstrates that a fully human anti-EGFR antibody (E7.6.3) blocks the binding of ligand to the EGFR and fully eradicates A431 tumor xenografts. According to the Examiner, although Yang fails to teach administration of the antibody to a human and that administration would be effective to inhibit the growth of refractory tumors, Prewett teaches that autocrine stimulation of EGFR by TGF-α may have relevance to the refractory nature of prostatic carcinoma to chemotherapy and suggests that antibodies to EGFR may provide a therapeutic intervention. The Examiner maintains that Prewett further teaches that A431 tumor xenografts are autocrine for production of TGF- α and, therefore, the A431 xenograft model used by Yang appears to be a good model for a refractory tumor. Thus, according to the examiner, "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the fully human anti-EGFR antibody of Yang for treatment of patients having refractory tumors. One would have had a reasonable expectation of success given the data supplied by Yang demonstrating the ability of the E7.6.3 antibody to totally eradicate the A431 tumor xenograft, which appears to be a good model for a refractory tumor." Applicant respectfully traverses the rejection.

Similarly, claims 34-36, 41-44, 48-51, 54 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Goldstein (Clinical Cancer Research 1:1311-1318 (1995);"Goldstein") in view of Prewett. The Office Action asserts that Goldstein teaches administering a chimeric anti-EGFR antibody (C225) to mice bearing A431

xenograft tumors and that the administration inhibited the growth of the xenograft. According to the Examiner, although Goldstein fails to teach administration of the antibody to a human and that administration would be effective to inhibit the growth of refractory tumors, Prewett teaches that autocrine stimulation of EGFR by TGF-α may have relevance to the refractory nature of prostatic carcinoma to chemotherapy and suggests that antibodies to EGFR may provide a therapeutic intervention. The Examiner maintains that Prewett further teaches that A431 tumor xenografts are autocrine for production of TGF- α and, therefore, the A431 xenograft model appears to be a good model for a refractory tumor. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the chimeric anti-EGFR antibody of Goldstein (C225) for treatment of human patients having refractory tumors, because Goldstein demonstrates that (i) the C225 antibody blocks the binding of ligand to EGFR and (2) the C225 antibody inhibits the growth of A431 xenograft tumors, which appears to be a good model for a refractory tumor. Applicant also respectfully traverses the rejection.

Applicant submits that the Office has not set forth a *prima facia* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966). Further, the prior art relied upon by an Examiner to establish a *prima facie* case must not only suggest that the claimed method be performed, but the prior art must also provide one of ordinary skill in the art with a reasonable expectation that the claimed subject matter can be successfully used to effect a practical purpose. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Refractory tumors, as recited in the pending claims, are those tumors that have failed to respond or become resistant to previous treatment with a chemotherapeutic or radiation therapy. The presence of such refractory tumors lead to rapid disease progression, usually with poor prognosis. Applicant asserts that, Yang in view of Prewett, or Goldstein in view of

Prewett, does not teach or suggest the presently claimed treatment of tumors that are refractory to treatment. Nor do the cited references provide one of ordinary skill in the art with a reasonable expectation that the claimed subject matter can be used to successfully treat refractory tumors.

The Examiner has attempted to rely on Prewett to cure the failure of Yang or Goldstein in teaching or suggesting the treatment of refractory tumors with the anti-EGFR antibody in humans. However, as explained below, the attempt has failed.

The Examiner states that "Prewett teaches that autocrine stimulation of EGFR by TGF- α may have relevance to the refractory nature of prostatic carcinoma to chemotherapy and suggests that antibodies to EGFR may provide a therapeutic intervention. (p. 5, Office Action). Accordingly, since Prewett also teaches that A431 cells are autocrine for the production of TGF-α the Examiner alleges that A431 cells are a "good model for refractory tumors." However, the Examiner's rationale relies on Prewett's ***speculation*** that "[t]he autocrine nature of ***metastatic*** prostatic carcinoma ***may*** have relevance to the refractory nature of the disease to chemotherapy..." (emphasis added; page 419, right column, the last three lines, Prewett). It should be noted that Prewett is basing this statement on the observed autocrine nature of ***late stage metastatic tumors*** and ***not on tumors that have become resistant to chemotherapy or radiation treatment, i.e, refractory tumors.***

In this regard, the statement of Prewett regarding the autocrine nature of metastatic prostate carcinoma is based on a study by Scher et al. (Clin. Cancer Research 1:545-550 (1995); "Scher"; Exhibit F) cited as Reference 17 in page 419 of Prewett. ***At the onset it should be noted that the prostate tumors studied by Scher were not tumors that had become resistant to chemotherapy or radiation therapy, i.e, refractory tumors.*** Rather, Scher found that naive prostate cancers, i.e., not subjected to prior hormonal therapy, had a paracrine relationship between EGFR and TGF-α, while androgen-independent prostate cancers, i.e., having progressive disease despite castrate levels of serum testosterone resulting from anti-androgen therapy, had an autocrine relationship between EGFR and TGF-α (see Abstract; page 545, right column, under "Patient Population"; page 546, left column, lines 2-8).

Moreover, Scher admits certain shortcomings in the study: "A **limitation of this study** was the unavailability of hormone-naive metastases.... Thus, the presence of the EGFR and its physiological ligand TGF-α in the evolution of androgen independence and its role in the metastatic process **requires further study**." (emphasis added; the paragraph bridging pages 548 and 549).

Accordingly, the studies of Scher, which Prewett relies on, do not relate to tumors refractory to chemotherapy or radiation therapy and, further, the importance of the presence of EGFR and TGF-α in the evolution of androgen independence in prostate carcinomas is unclear. An artisan of ordinary skill would not have concluded that there was a reasonable expectation that the therapeutic results of Yang or Goldstein on A431 xenograft tumors in mice could be extrapolated to the treatment of tumors refractory to chemotherapy and radiation therapy merely because A431 xenografts exhibit autocrine nature of EGFR and TGF-α..

Further, it should be noted that Prewett proceeds to describe experiments demonstrating that the A431 "human tumor cell line that expresses very high levels of EGFR...and is autocrine for the production of TGF- α" nevertheless responds to administration of anti-EGFR antibodies in the A431 xenograft model . (See, Prewett, p. 420, left col. second full paragraph). The A431 cells were not previously treated with chemotherapy or radiation therapy and there is no indication that the antibodies would be effective (or should be used) to treat tumors refractory to chemotherapy or radiation therapy. As previously mentioned, Prewett only offers conjecture and speculation concerning tumors refractory to chemotherapy and radiation therapy, underscoring that such tumors were not well understood. If anything, antibodies are only proposed as an alternative to prior chemotherapy or concurrent therapy. Further, there is no indication that the autocrine setting is indicative of a tumor refractory to chemotherapy or radiation therapy.

Rather, a number of published studies indicate that the A431 cells utilized in the xenograft tumor implants of Yang and Goldstein are ***not*** refractory cells, ***despite their autocrine nature.*** In this regard, the Examiner's attention is directed to a number of

published studies indicating that parental A431 cells are indeed sensitive to treatment with chemotherapeutic agents and that it is only after manipulation of the parental cell line that variants of the A431 cell line which are refractory to chemotherapy may be obtained. For example, parental A431 cells are normally found to be sensitive to cisplatin (Mese et al., 1998, Chemotherapy 44:414-420; "Exhibit C"), gefitinib (Yanese et al., 2004, Mol. Cancer Ther. 3:1119-1125: "Exhibit D"), and epoxomicin (Ohkawa et al., International Journal of Oncology 24:425-433; "Exhibit E").[1] In fact, as demonstrated in the xenograft studies set forth in Figure 2 of Mese (Exhibit C), parental A431 xenografts were found to be sensitive to chemotherapy, i.e, ***not refractory***, as demonstrated by the significant reduction in the weight of parental derived A431 tumors in cisplatin treated nude mice.

Since there is no indication in any of the references cited by the examiner that a A431 cell line other than the parental ***chemosensitive*** A431 cell line was used in the disclosed xenograft studies, such studies cannot be considered to suggest the claimed invention nor provide one of ordinary skill in the art with a reasonable expectation of successfully treating tumors refractory to chemotherapy or radiation therapy with an anti-EGFR antibody. Moreover, it is also noteworthy that ***none*** of the xenograft tumor implants disclosed in Yang or Goldstein were subjected to any treatment prior to administration of the anti-EGFR antibody. Thus, such xenograft tumors have not failed or been resistant to prior treatment as required by the currently pending claims.

Furthermore, at the time of the present invention, it was generally believed that anti-EGFR antibodies were ***cytostatic***, i.e, capable of inhibiting the proliferation cells, rather than ***cytotoxic***, i.e., capable of killing cells. Given that refractory tumors are those tumors that have failed to respond to agents known to be **cytotoxic** chemotherapeutic agents, one skilled in the art would not have reasonably believed that a cytostatic agent, such as an anti-EGFR antibody, could be used to successfully treat refractory tumors.

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[1] Chemoresistant A431 cells were only obtained after (i) selective growth in increasing doses of cisplatin or by mutagenic induction of resistance (Mese et al.,); (ii) genetic engineering of A431 cells to express a breast cancer resistance protein (Yanese et al.); or (iii) selective growth over a period of three months in increasing doses of epoxomicin (Ohkawa).

Thus, even if the combined references were to teach or suggest treatment of refractory tumors, there is no reasonable expectation that such combination treatment would be successful. One skilled in the art would not have been able to predict whether applicant's claimed invention would be effective until they had actually treated a patient with it. Accordingly, based on the teachings of the cited references taken together, there is no reasonable expectation that therapy using an anti-EGFR antibody, or fragment thereof, would be successful in treating refractory tumors that rises to the degree of predictability required for *prima facia* obviousness. A *prima facia* case of obviousness thus has not been established. In light of these remarks, applicant respectfully requests that the obviousness rejections be withdrawn.

DOUBLE PATENTING REJECTION

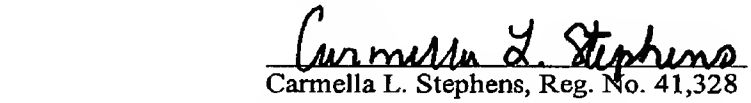
Claims 34-55 and 72 are provisionally rejected under the judicially created doctrine obviousness-type double patenting over Claims 34-56 and 72-87 of co-pending U.S. Patent Application Serial No. 11/018,950. Applicants take no position with respect to the provisional rejection at this time and reserve their rights with respect to both the present application and co-pending application. Nevertheless, Applicant is prepared to respond to the double patenting rejection by filing a timely terminal disclaimer in compliance with 37 C.F.R. 1.321 upon recognition of allowable subject matter.

CONCLUSION

In view of the foregoing amendments and remarks, it is believed that the subject claims are in condition for allowance, which action is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

In the event that the filing of this response is deemed not timely, applicant petitions for an appropriate extension of time. The petition fee can be charged to Deposit Account No. 11-0600.

Respectfully submitted,



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